REMARKS

Claims 12-14 and 37 are pending in this application. Claims 12-14 and 37 are rejected. By the present amendment the specification and claims 12, 13 and 37 are amended for clarity, and new claims 38 and 39 are hereby added. The specification is amended to add a sequence identifier for the mouse FGF1B promoter sequence as provided in GenBank Accession No. U67609, which sequence is now added to the attached sequence listing for inclusion in the present application. Support for the amendments to claims 12 and 37 and for new claims 38 and 39 is found on page 3, lines 22-28 and page 21, lines 7-10 of the application. As they are fully supported by the original specification, the amendments and new claims add no new matter.

In view of the above-described amendments and following remarks, reconsideration of claims 12-14 and 37, and consideration of new claims 38 and 39 are respectfully requested.

Compliance With CFR 1.821(a)-(d)

As requested by the Patent Office, Applicants have added the nucleotide sequence for the mouse FGF1B promoter as provided in GenBank Accession No. U67609 to the sequence listing for the present application. The GenBank Accession Number of the mouse FGF1B promoter was disclosed on page 7 of the application, and was publicly available at the time the present application was filed. In compliance with CFR 1.821 (a)-(d) applicants are submitting herewith a paper copy and a computer readable form (CFR) of the amended sequence listing. The paper copy and CFR are the same and add no new matter. In addition, Applicants have amended line 26 on page 7 of the instant specification to add the sequence identifier for the nucleotide sequence of the mouse FGF1B promoter as required by CFR 1.821 (a)-(d).

Section 103 Rejection

Claims 12 -14 and 37 are rejected under 35 U.S.C. § 103 as being unpatentable over Alam et al. (The Journal of Biochemistry. Vol. 271:30263-30271, 1996)(hereinafter "Alam et al.") or Ray et al. (The Journal of Biochemistry. Vol. 272: 7456-7555, 1997)(hereinafter Ray et al.) in view of Takahashi et al (Exp. Anim. 48: 255-261, 1999) (hereinafter "Takahashi et al.") and Perraud et al (Oncogene Vol. 7: 993-997, 1992) (hereinafter "Perraud et al.") and Ausubel et

al (Short Protocols in Molecular Biology. 3rd edition 1992, page 9-28-9-30, John Wiley and Sons. (hereinafter "Ausubel et al.").

None of the primary or secondary references applied by the Patent Office, either alone or combined, would motivate one of ordinary skill in the art to prepare a construct that comprises nucleotides -507 to + 1 of the human FGF1B promoter, operably linked to a sequence encoding the SV40 large T antigen as recited in amended claim 12 or to prepare a construct comprising the mouse FGF1B promoter, operably linked to a sequence encoding the SV40 large T antigen, as recited in amended claim 37. Alam et al. merely recites the sequence of the mouse FGF1 B promoter and that "FGF-1 message and its protein appears to be largely neuronal, with little or no glial component", and "that high levels of FGF-1B transcript occur in glioblastomas and glioblastoma-derived cell lines." (See page 30270, second full paragraph in column 2 of Alam et al.) Alam et al. provides no incentive for operably linking a sequence encoding the SV40 large T antigen to the human FGF1 B promoter as recited in claim 12 or to the mouse FGF1 B promoter as recited in amended claim 37, and, therefore, does not suggest such a combination. Moreover, Alam et al. does not teach or suggest that a construct comprising nucleotides -507 to + 1 of the human FGF1B promoter, operably linked to a sequence encoding the SV40 large T antigen or a construct comprising the mouse FGF1B promoter operably linked to a sequence encoding the SV40 large T antigen would lead to expression of the SV40 large T antigen in neural stem cells, as recited in amended claims 12 and 37, respectively.

Ray et al. recites constructs with portions of the FGF1B promoter linked to a nucleotide sequence that encodes luciferase. Ray et al. also provides information about the activity of these constructs in glioblastoma cells. Ray et al., however, does not teach or suggest replacing the luciferase encoding sequence with a sequence encoding the SV40 T antigen. Ray et al does not teach or suggest that such a modification would be desirable. Moreover, Ray does not teach or suggest that a construct comprising nucleotides -507 to + 1 of the human FGF1B promoter or the mouse FGF1 B promoter operably linked to the SV 40 T antigen would lead to expression of the SV40 T antigen in neural stem cells, as recited in amended claims 12 and 37.

Takahasi et al. does not provide the motivation that is absent from Ray et al. or Alam et al. The construct of Takahasi et al. does not include a tissue specific promoter, much less the FGF1 B promoter. Moreover, the construct of Takahashi does not include a sequence that encodes the SV40 large T antigen. Lacking a construct that comprises either of these, Takahasi

et al., alone or combined with Alam et al. and Ray et al., would not motivate one of ordinary skill in the art to operably link a sequence encoding the SV40 large T antigen to an FGF1 B promoter.

Perraud et al, also, would not motivate one of ordinary skill in the art to modify the FGF1B promoters recited in Alam et al. and Ray et al. by operably linking certain protions of such promoters with a sequence encoding the SV40 large T antigen as recited in amended claims 12 and 37. Perraud et al. recites a cystic fibrosis membrane conductance regulator (CTFR) promoter-SV40 T antigen fusion transgene, and transgenic mice comprising such a transgene. Perraud et al. indicates that the authors "expected that such an approach would permit the development of lung, pancreas and gastrointestinal epithelial tumors." (see, page 993, next to the last pargraph of column 2 of Perraud et al.) However, "surprisingly", the authors did not obtain such tumors. Id. Moreover, Perraud et al. provides at least four different possible reasons as to why the authors failed to detect SV40 T antigen protein in tissues such as the lungs and pancreas of the transgenic animals that they had produced using their transgene. (See bridging paragraph on page 996 of Perraud et al.) Thus, Perraud et al. clearly shows the unpredictability in the transgene art, particularly in transgenes containing a sequence encoding the SV40 large T antigen. As a result, one of ordinary skill in the art, upon reading Perraud et al., either alone or in combination with Ray et al. and Alam et al., would have no reason to believe that introduction of a transgene comprising an FGF1 B promoter operably linked to a sequence encoding the SV40 large T antigen would lead to expression of the SV40 T antigen in neural stem cells as recited in claims 12 and 37, as amended. In other words, Perraud et al. would not lead one of ordinary skill in the art to believe that the construct recited in claims 12 and 37 would work.

Ausubel et al. does not provide the motivation that is absent from Alam et al., Ray et al., Takahasi et al., and Perraud et al. Ausubel does not teach or suggest any construct comprising a sequence encoding the SV40 large T antigen, much less a construct comprising the FGF1B promoter operably linked to a sequence encoding the SV40 large T antigen. On page 9-29, Ausubel et al. shows a plasmid comprising the SV40 T intron. However, proteins such as the SV40 large T antigen are **not** encoded by introns. Proteins such as the SV40 large T antigen are encoded by exons.

In making the current rejection, the Patent Office has selected and combined the promoters recited in Alam et al. and Ray et al. with a sequence encoding an SV40 large T

antigen, a coding sequence that is found in the transgene of Perraud et al. However, to sustain a §103 rejection, it is not enough that one may modify a reference in view of a second reference. The modification cannot be considered obvious unless at least one of the prior art references suggests the desirability of the modification. Obviousness can not be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.

In its previous office action, mailed January 15, 2004, the Patent Office alleged that "an artisan would have been motivated to make such constructs because it would have allowed to study the brain specific expression of the FGF1B promoter and make cells or make cell lines or transgenic mice or rats which could provide in vivo model for studying promoter function." (See paragraph bridging page 5 and 6 of the January 15, 2004 Office Action.). Respectfully, these are the uses that are taught in the instant application. These uses are not suggested by the applied references. Two of the references applied by the patent office, namely Takahasi et al. and Ausubel, do not recite an FGF1B promoter OR a sequence encoding the large SV40 T antigen. A third applied reference, Perraud et al, suggests that combining a sequence encoding the SV40 large T antigen with the tissue specific CFTR leads to unexpected results, for which there are multiple possible but uncertain explanations. Neither the Alam, et al. or Ray, et al. overcome the unpredictability suggested by Perraud et al., i.e., that unexpected results occur when sequences encoding the SV40 large T antigen are operably linked to tissue specific promoters. Thus, the references applied by the Patent Office do not support its position. Lacking such support, the § 103 rejection is improper and should be withdrawn.

Applicants submit that claims 12-14 and 37, and new claims 38 and 29 are now in condition for allowance. Prompt notice of such allowance is respectfully requested.

Respectfully submitted,

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By: Pamela A. Docherty

Pamela A. Docherty, Reg. No. 40,591
(216) 622-8416